Appendix 5

The Cost of Prostate Cancer Chemoprevention: A Decision Analysis Model

Robert S. Svatek,[1] J. Jack Lee,[2] Claus G. Roehrborn,[1] Scott M. Lippman,[2] and Yair Lotan[1]

The University of Texas Southwestern Medical Center, Dallas, Texas and [2]The University of Texas M.D. Anderson Cancer Center, Houston, Texas

Abstract

Background: The Prostate Cancer Prevention Trial found reduced prostate cancer prevalence for men treated with finasteride. The public health cost of wide-scale chemoprevention is unclear. We developed a model to help clarify the cost effectiveness of public use of prostate cancer–preventive agents.
Methods: A Markov decision analysis model was designed to determine the lifetime prostate health-related costs, beginning at the age of 50 years, for men treated with finasteride compared with placebo. Model assumptions were based on data from the Prostate Cancer Prevention Trial, a literature review of survival and progression rates for patients treated with radical prostatectomy, and costs associated with prostate cancer disease states.
Results: Chemoprevention with finasteride resulted in a gain of 13.7 life years per 1,000 men at a cost of $704,000 per life year saved (LYS). However, if finasteride is assumed to not increase the incidence of high-grade tumors, it renders a gain of 21.4 life years per 1,000 men at a cost of $434,000 per LYS; finasteride must cost $15 monthly to reach $100,000 per LYS. When applied to a population at higher risk (lifetime prevalence of ≥30%) for developing prostate cancer, the cost of finasteride must be reduced from its current cost ($62/mo) to <$15 per month for the cost effectiveness to fall below $50,000 per LYS.
Conclusions: Given the natural history of treated prostate cancer, implementation of chemoprevention would require an inexpensive medication with substantial cancer risk reduction to be cost effective. Targeting populations at higher risk for developing prostate cancer, however, allows for considerable flexibility in the medication cost to make prostate cancer chemoprevention a more attainable goal. (Cancer Epidemiol Biomarkers Prev 2006;15(8):1485–9)

Introduction

The NIH estimated that the overall economic cost of cancer in the United States was $189.8 billion in 2004, with $69.4 billion attributed to direct medical costs, $16.9 billion to indirect morbidity costs, and $103.5 billion to indirect mortality costs (1). Prostate cancer is the most common nonskin malignancy and the second leading cause of cancer death among men in the United States (2) An estimated 232,090 new cases of and 30,350 deaths from prostate cancer occurred in the United States in 2005 (1). Therefore, effective prostate cancer prevention could substantially reduce overall cancer-related costs in the United States.

The Prostate Cancer Prevention Trial (PCPT) examined the ability of finasteride to prevent prostate cancer in 18,882 men who were 55 years or older (3). Finasteride inhibits 5α-reductase from metabolizing testosterone into the more potently carcinogenic androgen dihydrotestosterone and thus lowers the level of dihydrotestosterone in the prostate. PCPT participants were randomized to finasteride or a placebo and then treated and followed for 7 years. The 7-year prevalence of prostate cancer was reduced by 24.8% in the finasteride versus in the placebo group. However, there also was an increase in high-grade prostate tumors (Gleason score of ≥7) in the finasteride compared with the placebo group (37% versus 22.2%). This high-grade finding of the PCPT has complicated the assessment of competing benefits, risks, and costs and thus prevented the community-wide acceptance of finasteride for prostate cancer prevention. Indeed, no drug has been approved by the U.S. Food and Drug Administration for prostate cancer prevention to date.

We designed the current study to develop a model that can assess the financial effect on society of the public health use of a prostate cancer–preventive agent, such as finasteride, by millions of men at risk.

Materials and Methods

Markov Decision Analysis. A Markov decision analysis model was created to compare the lifetime cost associated with treating men at risk for prostate cancer with finasteride versus without finasteride. The model was designed to compare the financial effect of this cost on the public. Similar to the PCPT entry criteria, the base case was assumed to have a prostate-specific antigen (PSA) of ≤3.0 mg/mL, a normal digital rectal exam, and an American Urological Association symptom score of <20 (3). The base case is a 50-year-old man who receives daily finasteride treatment for a total of 20 years or until prostate cancer is diagnosed. As shown in Fig. 1, we assumed a simple model of disease progression that occurred in a fixed sequence of health states: (a) cancer free, (b) prostate cancer (Gleason grades 8-10, 7, 6, or 2-5), (c) biochemical recurrence of prostate cancer, (d) metastatic disease, and (e) death. At the conclusion of each 12-month cycle, the patient could remain in the same health state, experience progression of their disease, or die of unrelated causes. Following the diagnosis of cancer, the patient undergoes immediate radical retropubic prostatectomy and pelvic lymph node dissection without adjuvant or neoadjuvant therapy. Biochemical recurrence, when present, was managed initially with watchful waiting. No patient received early hormone ablative therapy. If the patient entered the metastatic disease health state, it was assumed that he would be treated with androgen ablation therapy using leuprolide acetate. No additional costs were added for potential use of chemotherapy because chemotherapy use is inconsistent in patients with androgen-independent prostate

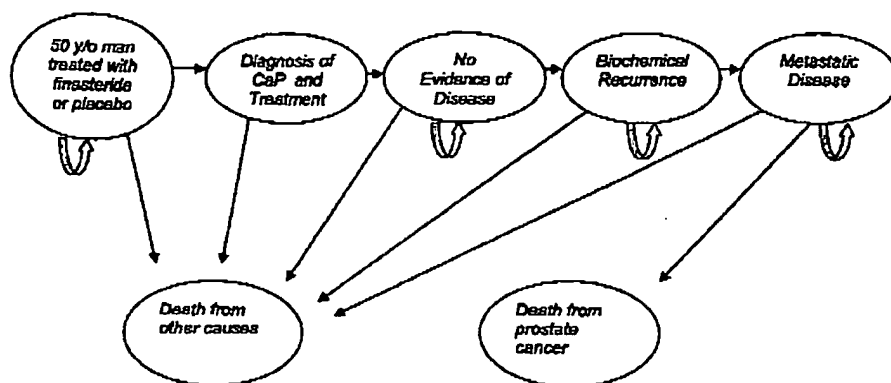**1486 The Cost of Prostate Cancer Chemoprevention**

Figure 1. Markov cycle. Circles, various Markov states in the model. Arrows, transitions between disease states. Transition probabilities are shown in Table 1. CaP, prostate cancer.

cancer. However, an additional analysis was conducted after applying cost for salvage therapy and chemotherapy for a large number of patients diagnosed with prostate cancer. We assumed a quarter of men with prostate cancer diagnosis received salvage therapy following PSA recurrence at a cost of $15,000 and one half of men with metastatic disease received chemotherapy at a cost of $50,000. Markov modeling was designed with TreeAge Pro Healthcare (4). The lifetime cost for chemoprevention is defined as the lifetime cost of preventive medication plus the lifetime cost of prostate cancer care considering the reduced risk of developing any prostate cancer and the increased risk of developing high-grade prostate cancer on finasteride. The lifetime cost of the placebo arm is just the lifetime cost of prostate cancer treatment considering the increased risk of developing any prostate cancer and reduced risk of developing high-grade prostate cancer versus finasteride. The cost per life year saved (LYS) is the difference between the lifetime costs for the chemoprevention group and placebo group divided by the gain of life years.

Assumptions

Prostate Cancer Incidence. The prostate cancer incidence for men was based on for-cause biopsy detection rates (and excluded cancer detected in end-of-study biopsies, which were not for cause) in the placebo arm of the PCPT (3). To estimate the age-specific incidence rates for men not represented in the PCPT (age <55 years) and to determine lifetime prostate cancer incidence rates, a smooth isotonic regression curve was applied to the age-specific detection rates observed in the PCPT. Incidence rates among finasteride-treated men were derived from the placebo arm detection rates after applying a yearly relative risk reduction afforded by finasteride. Based on these factors, the estimated average lifetime probability of developing prostate cancer is 12.5% with finasteride versus 16% without finasteride. In the PCPT, men treated with finasteride were found to have an increased distribution of higher grade tumors compared with men in the placebo arm. However, there is some evidence that this distribution may be a grading bias (5-7). Therefore, we did an analysis with and without a difference in Gleason score distribution.

Outcomes Following Treatment of Prostate Cancer. The long-term progression and survival rates for patients treated with radical prostatectomy are based on literature about the natural history of treated prostate cancer (Table 1; refs. 8, 9). To approximate the outcomes of men from the PCPT, we used publications characterizing outcomes among patients with low-stage disease (T1c and T2a-b) in the PSA era when available.

Costs. Cost data are shown in Table 2 (10-14). All data were collected from cost, not charge, data. All costs were updated to 2005 U.S. dollars with the Gross Domestic Product Deflator Inflation Calculator (15). An annual discount rate of 3% was applied to future costs and future years of life (16, 17). Discounting is necessary when the experience of the patient in the near term is valued more than future costs and health outcomes (18). Medication costs were based on average manufacturer's wholesale drug price. The cost of finasteride was based on current costs at a nationwide pharmacy (ref. 19; $62/mo) and this cost accumulated until the patient was diagnosed with prostate cancer, died from other causes, or reached 70 years of age.

Cost of radical retropubic prostatectomy included the costs of hospitalization and the cost of immediate and late complications (20). Prostate cancer–related costs depend on the patient's disease status. Following retropubic prostatectomy, costs include follow-up physician visits and PSA laboratory tests. Yearly costs associated with PSA recurrence and metastases are shown in Table 2.

Effect of Finasteride on Benign Prostatic Hyperplasia. The risk reduction afforded by finasteride for preventing benign prostatic hyperplasia was based on data from the Medical Therapy of Prostatic Symptoms Trial (21). Average treatment cost for men with benign prostatic hyperplasia was based on treatment costs, including medical and surgical therapy.

Sensitivity Analysis. Sensitivity analysis was done to investigate the effect of adjusting several of the base case assumptions. Prostate cancer incidence rates found in the PCPT were used for the model to reflect a scenario of chemoprevention for men without prostate cancer at the onset

Table 1. Transition probabilities for different health states

Gleason score	No evidence of disease to biochemical recurrence, y (8)			Biochemical recurrence to metastatic disease, y (9)		Metastatic disease to prostate cancer death, y (9)	
	5	10	15	5	10	5	10
8-10	0.25	0.43	0.50	0.625	0.8125	0.50	0.875
7	0.21	0.35	0.42	0.25	0.5	0.50	0.875
6	0.15	0.25	0.31	0.25	0.5	0.50	0.875
2-5	0.12	0.20	0.23	0.25	0.5	0.50	0.875

Table 2. Assumptions on model variables, including costs of medication, disease status, treatment procedures, visits, and tests with additional assumptions on the prevalence and effectiveness of finasteride on benign prostate hypertrophy

Variable	Base case	Range in sensitivity analysis
Medications (annual costs, U.S. dollars)		
Finasteride (19)	749	713-959
Leuprolide acetate (11)	5,709	2,317-8,111
α Blocker (19)	432	288-840
Disease states (annual costs, U.S. dollars)		
Biochemical recurrence (11)	371	231-927
Metastasis (11)	463	231-927
Other (one-time cost, U.S. dollars)		
Cost of terminal care for prostate cancer (11-13)	40,744	6,714-47,601
Radical retropubic prostatectomy (20)	18,000	15,675-21,020
Complications from retropubic prostatectomy (20)	2,445	1,500-4,000
Physician visit*	60	50-100
PSA laboratory test*	7	6-60
Transurethral resection of prostate*	4,597	
Prevalence of benign prostatic hyperplasia (14)		
Age <65 y	0.15	0.10-20
Age ≥65 y	0.22	0.14-30
Relative effect of finasteride on prevalence of benign prostatic hyperplasia, % (3)	60	50-100
Discount Rate, % (16, 17)	3	1-5

*Local cost estimates.

of intervention. We did sensitivity analyses following adjustment of the cost and risk reduction provided by finasteride. In addition, chemoprevention for high-risk populations, such as men with a family history of prostate and/or men with high-grade prostatic intraepithelial neoplasia, may be more cost effective because of the increase prevalence of the disease. We examined the effects of adjusting the prevalence of prostate cancer in the population.

Results

Reduced Overall, Increased High-Grade Prostate Cancer with Finasteride. Our first analysis assumed the grade distribution of the PCPT-reduced overall prostate cancer and increased high-grade prostate cancer in the finasteride versus the placebo arm (3). Under this assumption, finasteride chemoprevention resulted in a gain of 13.7 life years per 1,000 men. At an increased lifetime cost of $9,631 per person, this renders a discounted incremental cost effectiveness ratio of $703,847 per LYS for finasteride versus no treatment.

Reduced Overall, No Increased High-Grade Prostate Cancer with Finasteride. Based on evidence that the higher distribution of Gleason score of ≥7 in the finasteride versus the placebo arm of the PCPT may have been more apparent than real, our second analysis assumed that finasteride reduces overall prostate cancer and does not increase the incidence of high-grade disease. Under this assumption, finasteride chemoprevention resulted in a gain of 21.4 life years per 1,000 men. At an increased lifetime cost of $9,607 per person, this renders a discounted incremental cost effectiveness ratio of $434,113 per LYS for finasteride versus no treatment.

Sensitivity Analysis. A two-way sensitivity analysis relaxing the assumptions about the disease prevalence and the relative risk reduction in the incidence of prostate cancer is shown in Table 3. Assuming a 25% relative risk reduction

afforded by treatment, if the cost of finasteride was reduced from its current cost of $62 per month to $15 per month, the cost per LYS would fall to $52,908 for a population at high risk (prevalence of ≥30% for men age 50 years and older) of developing prostate cancer. On the other hand, at a cost of $62 per month, a relative risk reduction of 50% targeted at a population with a prostate cancer prevalence of ≥35% after the age of 50 years would be required to obtain a cost of $100,000 per LYS. Graphic representations of two-way sensitivity analyses are shown in Figs. 2 and 3. Figure 2 shows that disease prevalence and the prostate cancer risk reduction significantly affect the cost effectiveness of finasteride. At a cost of $62 per month, the cost per LYS is >$100,000 unless the prevalence is >40% and the risk reduction is >50%. In Fig. 3, cost effectiveness is based on varying drug costs and disease prevalences. At low drug costs, chemoprevention results in <$100,000 per LYS even at low disease prevalence. An additional analysis was done to bias toward an increased cost of prostate cancer treatment. We assumed a quarter of men with prostate cancer diagnosis received salvage therapy following PSA recurrence and one half of men with metastatic disease received chemotherapy. This resulted in a decrease in the cost effectiveness ratio by 3.9%.

Discussion

Finasteride produced a 24.8% reduction in prostate cancer prevalence over a 7-year period in the PCPT. The PCPT, however, also found an increased risk of high-grade disease with finasteride, which has prevented the widespread use of this agent for preventing prostate cancer. Competing benefits, risks, and costs have emerged as the major issue governing preventive agent use, and we conducted the present analysis to explore the potential effect of finasteride or any other prostate cancer prevention agent on cancer costs in the United States.

Our analysis shows that finasteride at its current cost ($62/mo) would result in a significant economic burden to society if taken by all men starting at the age of 50 years. Based on 2004 census figures, the United States has >28 million men over the age of 50 years (http://www.census.gov), and introducing a medication costing $62 per month would add billions of dollars to public health costs. The estimated "reasonable" costs per LYS fall in a wide range. In a review of cost effectiveness analyses, Earle et al. (22) noted that most studies did not specify a standard reasonable cost per LYS and that the minority of studies specifying a cost pegged it at no >$100,000 per LYS, far below the modeled finasteride costs of $703,847 per LYS (assuming increased high-grade prostate cancer with finasteride) or $434,113 per LYS (assuming no increased high-grade disease with finasteride). In analyzing the cost effectiveness of tamoxifen for high-risk women based

Table 3. Three-way sensitivity analysis assuming similar grade distribution between finasteride and placebo arms

Relative risk reduction (%)	Cost of finasteride (U.S. $/mo)	Lifetime prevalence (men diagnosed after the age of 50 years)			
		12.5% ($)	30.0% ($)	40.0% ($)	50.0% ($)
25	15	92,413	52,908	39,941	29,883
	30	211,183	117,224	86,141	61,630
	62	467,857	256,218	185,982	130,238
50	15	37,411	19,233	13,299	8,743
	30	91,753	48,435	34,133	22,901
	62	209,191	111,544	79,159	53,498
80	15	20,855	9,024	5,152	2,166
	30	55,864	27,681	18,361	11,019
	62	131,521	68,001	46,907	30,151

NOTE: Results are cost per LYS.

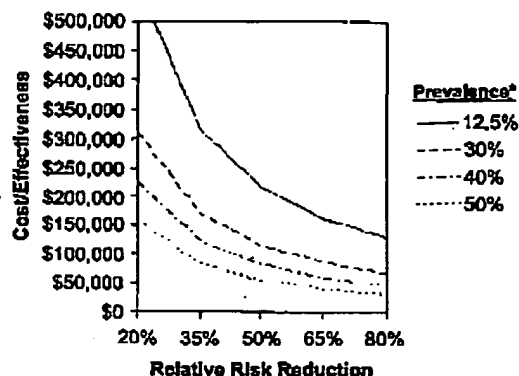**1488** The Cost of Prostate Cancer Chemoprevention

Figure 2. Two-way sensitivity analysis. Effect of relaxing assumptions about relative risk reduction and prevalence assuming finasteride cost of $62 per month. *Asterisk*, prevalence of prostate cancer ≥50 years of age.

on the Breast Cancer Prevention Trial, Hershman et al. (23) identified subgroups, in which the cost per LYS was <$50,000. The costs of finasteride and other chemoprevention agents would drop below $50,000· per LYS if used in higher risk populations and/or at lower costs as shown in Table 3. Our analysis was based on a societal perspective, and considerations for an individual at risk for prostate cancer may be quite different. Many people, especially those at a higher risk, may be willing and able to pay out-of-pocket for a chemopreventive agent with a showed prostate cancer risk reduction. A national survey documenting the prevalence and costs of alternative medicine use in the United States found that an ~15 million adults or 18.4% of all prescription users took prescription medications concurrently with herbal remedies and/or high-dose vitamins in 1997 (24). Estimated expenditures for alternative medicine professional services were conservatively estimated at $21.2 billion in 1997, with at least $12.2 billion paid out-of-pocket. Because most alternative medications have not been tested rigorously in randomized, controlled trials, it is not unreasonable to assume that rigorously evaluated medications shown to reduce cancer will be welcomed by people at risk (25). Although a medication, such as finasteride, may not be accepted due to concerns over high-grade disease, future medications may appeal to individual patients even if not cost effective from a public health standpoint.

The proportions of high-grade (Gleason score of ≥7) tumors in the PCPT were 37% in the finasteride arm and 22.2% in the placebo arm. Although certain data suggest that this finasteride-associated increase in high-grade tumors may be due to a grading bias and not to truly advanced disease, this issue is unsettled. The distribution of Gleason scores was important, however, in the survival advantage and overall cost benefit of finasteride treatment in our model. Our analysis indicates that with the Gleason score distributions found in the PCPT, finasteride could be expected to offer a survival benefit of 0.28 month per individual (versus placebo). Assuming that finasteride does not truly increase high-grade tumors, however, we found that the survival advantage would be 1.2 months per individual. This survival advantage translates into a substantial benefit if it is averaged across the population targeted for chemoprevention. For example, tamoxifen was found to reduce the risk of breast cancer by 50% in a high-risk population (26) and approved by the Food and Drug Administration for reducing the risk of primary invasive breast cancer among women at high risk (27). Survival outcome modeling of Breast Cancer Prevention Trial results found that tamoxifen could increase survival by 2.3, 1.4, and

0.9 months for individuals initiating tamoxifen at ages 35, 50, and 60 years, respectively (23).

In a previous examination of the implications of the PCPT (28), we used previously published data based on long-term outcomes for men with prostate cancer to determine the survival benefit conferred by chemoprevention with finasteride over a 15-year period. As in this analysis, we found a small but significant benefit from treatment with finasteride with population-wide gains in survival of <2 months per individual assuming no increase in high-grade cancers from finasteride. The use of Markov modeling, however, allows for a more accurate estimate of the net gains in chemoprevention. Markov modeling allows for incorporating distinct transition rates for various stages of disease based on data from patients with staging and grading characteristics similar to those in the PCPT. In addition, the model can account for lifetime benefits, including those gained or lost near the end of life. Furthermore, the present model included the time from initiating finasteride to the diagnosis of prostate cancer (based on age-specific incidence rates of the PCPT), which was not included in our previously published analysis.

The results of our study are similar to those recently reported by Zeliadt et al. (29), who also found that finasteride was not cost effective for men age 55 years or older at a cost of $233,000 per LYS assuming that finasteride prevents 25% of both high- and low-grade cancers. In the Zeliadt analysis, the prostate cancer incidence rates were based on Surveillance, Epidemiology, and End Results data. In contrast, we used incidence rates found in the PCPT to appropriately estimate rates that might be found in a population more heavily screened than the Surveillance, Epidemiology, and End Results population. Despite using different incidence rates, both models indicate that only a small proportion of the overall population develops prostate cancer. Therefore, a substantial portion of the cost is generated by giving finasteride to men who would never develop prostate cancer without finasteride. Even when applying cost for salvage therapy and chemotherapy to a large percentage of patients diagnosed with prostate cancer in our model, the cost effectiveness from finasteride changed minimally.

The benefit of a preventive intervention depends in part on the baseline risk of the population receiving it. To examine the effects of applying a chemoprevention strategy within a selected population at high risk, we did a sensitivity analysis by adjusting disease prevalence. Applying chemoprevention to a high-risk group, such as men with high-grade prostatic intra-epithelial neoplasia or men with a family history of prostate cancer, would improve the cost effectiveness ratio. Therefore, this model can be used in determining appropriate target
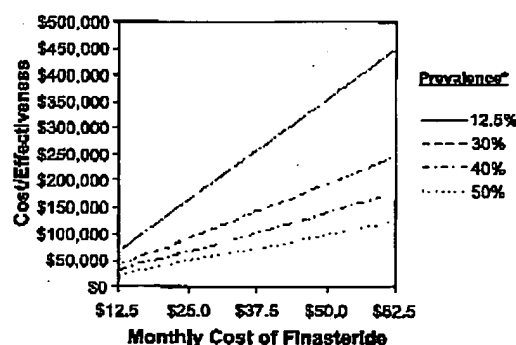

Figure 3. Two-way sensitivity analysis. Effect of relaxing assumptions about monthly cost of finasteride and prevalence assuming risk reduction 25%. *Asterisk*, prevalence of prostate cancer ≥50 years of age.

populations for chemoprevention strategies. This sensitivity analysis, however, assumes that finasteride would produce the same relative risk reduction in lower- or higher-risk populations, which is speculative. As our ability to identify high-risk populations improves and as new chemopreventive agents are discovered, it is quite possible that cost-effective agents will become available. Certainly, when the patent on finasteride ends, the cost of the drug will decrease and the cost effectiveness ratio will significantly improve, possibly making finasteride prevention in certain high-risk populations economically beneficial.

Our analysis has certain limitations. Alternative treatment modalities for the primary management of prostate cancer may vary significantly in cost. Timing and method of hormone ablative therapy can considerably affect the financial burden of the disease. In addition, other costs important from a societal perspective, such as loss of productivity or travel, were not considered. Some inaccuracy of cost and transition rates, however, is unavoidable given the variability of different practice patterns, local costs, and differences in prostate cancer outcome found in published series. For the most part, we chose the highest estimates of the cost available in terms of treatment or living with the disease to bias toward favoring treatment with finasteride. In addition, the duration of the effect from finasteride is unknown because the PCPT only evaluated patients for 7 years. We modeled the use and risk reduction of finasteride over a 20-year period (beginning in men ages 50 years old) because age 70 years is typically the cutoff used for prostate cancer screening.

In conclusion, finasteride, at its current cost, would not be cost-effective prostate cancer prevention for a population of lower-risk men ages 50 years or older. Targeting higher-risk populations, however, would increase the cost at which finasteride would become cost-effective prevention. A major current direction of prostate cancer prevention study is the development of models based on molecular and other factors that can identify high risks of prostate cancer, particularly aggressive prostate cancer (10). This work promises to make cost-effective prostate cancer chemoprevention an attainable goal.

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